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Highlight

A promiscuous interaction of SARS-CoV-2 with bacterial products

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SARS-CoV-2 is the virus responsible for COVID-19 disease, and since its emergence it has spread globally with the number of total cases in the tens of millions. COVID-19 presents with varied clinical manifestations that range from asymptomatic disease to severe respiratory disease (pneumonia) with multiple organ failure and death. Several risk factors have been associated with severe COVID-19 disease such as age, gender, diabetes, cardiovascular disease, treatments, and comorbidities that affect the immune system (Harrison et al., 2020). As is often the case for pathogen infections, the host immune system is a key player in virus clearance and resolution of disease. Nevertheless, a wealth of evidence has emerged to implicate the host's immune system in the outcome of disease severity. In this case, an imbalance between inflammation and protection leads to the progression to more severe disease.

The progression to severe disease is marked by a 'cytokine storm' with high levels of IL-1B, IL-6, TNF, and IL-1RA (Mangalmurti and Hunter, 2020; Moore and June, 2020). This is accompanied by a reduction of the number of circulating lymphocytes (CD4, CD8, and innate lymphocyte populations), as well as a reduction of monocytes and dendritic cells and respective activation markers in severe cases (Carissimo et al., 2020; Silvin et al., 2020). Multiple hypotheses have arisen to explain this phenomenon such as the infiltration of immune cells in the infected organs (i.e. lung) as well as potential nonproductive infection of immune cells that could trigger dysregulation such as higher proinflammatory signals and exacerbated apoptosis. To date, no mechanism has been identified as the trigger of the cytokine storm during SARS-CoV-2 infection.

The study by the laboratory of Dr Schmidtchen disclosed a very interesting discovery (Petruk et al., 2020). Using various complementary approaches such as native gel separation and microscale thermophoresis assay, the authors have shown that the envelope glycoprotein of SARS-CoV-2 (Spike) and of SARS-CoV (responsible for the 2003 SARS epidemic) is able to bind to lipopolysaccharide (LPS) of *Escherichia coli* and to lipid A—the toxic portion of LPS and conserved within Gram-negative bacteria. They have observed that Spike protein was able to bind to LPS with a similar affinity as CD14, the receptor used by immune cells to capture LPS and transfer it to the toll-like receptors for inflammatory signalling. Next, in order to evaluate whether Spike protein binding LPS had any physiological relevance during disease, the authors elegantly showed that the combination of low concentration of Spike and LPS having minimal effect by themselves was able to induce a strong activation of the NF-κB promoter activity. They observed this potentiating effect of Spike on LPS signalling *in vitro* in human reporter cell lines and primary peripheral mononuclear cells, as well as *in vivo* in a NF-κB reporter mice system. Of note, a dysregulated NF-κB activation is known to be a key pathogenic processes of various inflammatory diseases, since it controls the promoter activity of multiple proinflammatory cytokines (Liu et al., 2017).

This discovery by the laboratory of Dr Schmidtchen raises very intriguing possibilities as a potential trigger mechanism for the cytokine storm seen in COVID-19 patients, especially since the incidence of Gram-negative coinfection in severe cases is high (Petruk et al., 2020). Indeed, in animal models, LPS injection to mimic Gram-negative infection is sufficient to trigger a cytokine storm (Mangalmurti and Hunter, 2020). It is, therefore, possible that SARS-CoV-2 has evolved to bind to LPS to induce a strong proinflammatory response beneficial for viral replication or immune evasion. However, there are multiple other evolutionary pressures that could explain the binding of LPS to the Spike protein (Figure 1). One could hypothesize from examples in the literature that, similar to reoviruses, this interaction could influence Spike thermal stability allowing the viral particle to resist a wider range of temperatures (Berger et al., 2017). This interaction could also allow coronavirus

binding to bacteria promoting the delivery of multiple particles to a single cell similar to polioviruses (Erickson et al., 2018). Furthermore, it is also possible that this interaction impacts the tropism of SARS-CoV-2, similar to the mechanisms on Noroviruses (Jones et al., 2014; Baldridge et al., 2015).

This discovery opens up novel avenues of research into the mechanisms behind this interaction in order to elucidate the impact on the varied COVID-19 symptom manifestations as well as SARS-CoV-2 transmission.

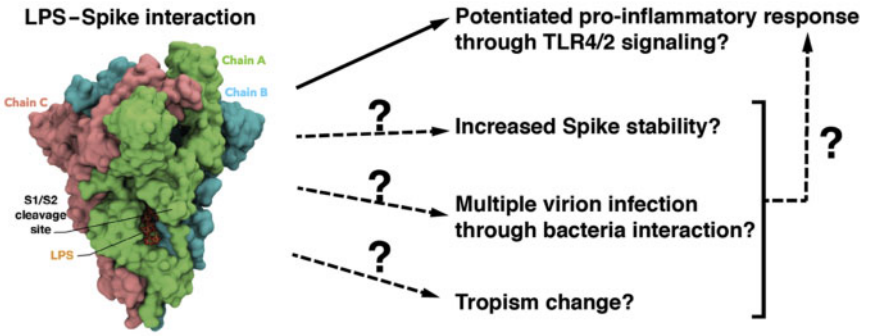

Figure 1 Schematic representation of the possible consequences of LPS–Spike interactions.

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